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January 26, 2005

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852.

RE: Criteria for Safety and Efficacy Evaluation of Oxygen Therapeutics as Red Blood Cell Substitutes, Guidance for Industry; Docket No. 2004D-0462, CBER 200114.

Dear Docket Officer:

America's Blood Centers (ABC) appreciates the opportunity to comment on the Center for Biologics Evaluation and Research's (CBER) draft guidance. We understand that our comments are public information and may be posted to the FDA Web site or otherwise made available. For your information, ABC is a national network of locally-controlled, not-for-profit community blood centers that collect and provide almost half of the US volunteer donor blood supply.

ABC supports CBER's intent to license oxygen therapeutics as red blood cell substitutes, especially in the trauma setting. In this setting, licensed oxygen therapeutics could save lives now lost due to the difficulty of providing transfusions before a patient reaches the hospital. They could add to the 'golden hour,' alleviate patient mortality, and reduce the risk associated with uncrossmatched blood. Moreover, by decreasing the current high demand on O negative blood for trauma patients, the availability of oxygen therapeutics for trauma could increase the availability of O negative blood – especially for women of child bearing age.

Our specific comments on the draft guidance follow:

IV. A.2. Recommendations. Preclinical Evaluation. Animal Safety Testing.

Evaluation of Immune Responses to Oxygen Therapeutic Products.

"We recommend that you test for an immune response to the product, e.g., development of IgG or IgE response to product administration or appearance of delayed hypersensitivity on repeated exposure."

Comment: We agree that it is important to consider the immunogenic potential of the products and the effects if/when humoral or cellular immunity changes.

Important Observations in Animal Tests.

"We suggest that you perform studies in a primate model to evaluate cardiac toxicity. Such a model should be sensitive to detecting degenerative changes in cardiac myocytes. Histologic evaluation of sections of myocardium should include papillary muscle and interventricular septum including the conduction system. In particular, we would highlight the difficulties in determining which treatment paradigm to use. The accepted protocols include top loading the red blood cell substitute infusion or exfusing the animal while infusing product. Each has its inherent problems which could impact a toxicity assessment

regardless of species studied. Early studies of substitutes in primates did show histologic evidence of myocardial lesions cardiac changes in animal studies also included dog models. Given the economic and ethical issues of doing primate studies we believe the requirement for non-human primnate studies which require sacrificing the animal and post-mortem examination will restrict the development of new Oxygen therapeutics and/or the refinement of materials currently under investigation.

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Comment: We believe that the requirement for a primate model to assess cardiac toxicities will be prohibitively difficult and expensive.

ABC Recommendation: We suggest that mammals other than primates (*e.g.*, dogs and/or pigs) be evaluated to be used for these studies.

[Interference of hemoglobin solutions with measurements of clinical laboratory parameters.]

"We recommend that you evaluate and resolve interference of hemoglobin solutions with measurements of clinical laboratory parameters for all relevant clinical laboratory instrumentation. Colorimetric interference with a number of clinical laboratory assessments that are important for individual patient management may occur with hemoglobin-based oxygen therapeutics. Manufacturers of oxygen therapeutics should anticipate ongoing support of clinical laboratories and evaluation of the effects of either hemoglobin-based oxygen carriers or perfluorochemical emulsions on new instruments or methods of analyte determination."

Comment: We applaud the inclusion of the recommendation for addressing confounding effects on clinical laboratory tests, since these effects will challenge the typical laboratory to come up with alternate test methods.

IV. B. 1. Recommendations. Clinical Evaluation. General.

"We recommend a clinical development plan that includes safety and efficacy assessments in both trauma and elective surgical settings to gain a full understanding of the adverse event profile of an oxygen therapeutic. We believe an evaluation in both trauma and elective surgery will provide a full understanding of both the benefits and the risks of oxygen therapeutic use in the broadest spectrum of situations in which such products may be used."

Comment: CBER appears to be asking the manufacturers to provide data for a specific oxygen therapeutic in both elective surgical and trauma settings. The agency acknowledges that the study size will likely be very large to answer the safety and comparability questions. The requirement to conduct trials in both settings will vastly increase the costs of the trials and may preclude some promising oxygen therapeutics from being licensed. To date, no one company has been able to address all of these clinical settings in a way that has been close to satisfactory.

We understand CBER's need to assure that any oxygen therapeutic approved for marketing is safe and effective. In addition, we understand the agency's concerns about "off-label" use. However, some of the recommendations will require clinical trials of such scope and expense that many promising products may be unable to proceed to potential licensure. We urge CBER not to raise the bar so high as to create a barrier against the availability of oxygen therapeutics in the trauma setting.

We are concerned that there is little or no consideration of the use of oxygen therapeutics as a bridge to transfusion in patients with limited transfusion options due to allo-immunization, patients with autoimmune hemolytic anemia or sickle cell disease or for patients' whose religious preferences deny them red blood cells. Although these uses may not affect a large proportion of patients, they are likely to be life-saving for some patients, and indications for their use should be discussed and considered in the guidance.

ABC Recommendation: Good data from the trauma or the elective surgery setting should be separately evaluated and, if appropriate, a product should be licensed for a single indication. Concerns about off-label use may be addressed by requiring prominent "cautions" and "warning statements" on the product label. "Off-Label" use of the product as a bridge for the patient groups mentioned above would be a continuation of the policies that have governed past decisions of the agency and the company regarding compassionate use. The guidance should be worded to allow the use of the product in those specific life-saving instances in the absence of clinical trial data for each and every possible indication.

Thank you for the opportunity to comment. I would be pleased to answer any questions you may have.

Yours truly,

Judith Woll, M.D.
Chair, Scientific, Medical and Technical Committee
America's Blood Centers